Predictors of the outcome of the Oral Food Challenge for Cow's Milk Protein Allergy: raw vs. processed foods

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ABSTRACT

Objectives: To describe the population of children with IgE-mediated CMPA tolerant to processed or raw CMP in the OFC, comparing their clinical, epidemiological and laboratory characteristics and evaluating the possible predictors of outcomes associated with these different presentations of CMP. **Methods:** Cross-sectional study carried out in an allergy clinic of a tertiary hospital in Fortaleza, Ceará. Data collection was carried out between October 2018 and September 2019. The questionnaire was filled out with epidemiological, clinical and laboratory data found in the medical records. The total sample was composed of 49 children with IgE-mediated CMPA tolerant to processed or raw foods in the OFC. **Results:** The comparison of the clinical and epidemiological characteristics of populations tolerant to raw foods vs. processed (respectively) showed similarities, such as the predominance of the male gender (60% vs. 57.9%); mixed ethnicity (73.3% vs. 68.4%); delivery at term (80% vs. 77 .8%); no complications during pregnancy (58.3% vs. 80.0%) or childbirth (70% vs. 78.9); mean maternal age (32 years vs. 35 years); level of education of the mothers (complete high school - 43.3% vs. 47.4%); age of onset of CMPA symptoms between 1 and 6 months (76.7% vs. 68.4%); exclusive breastfeeding for 4 to 6 months (60% vs. 68.45%); family history of food allergy (73% vs. 68.4%); and respiratory (38.9% vs. 35.7%) and food allergies (38.9% vs. 35.7%) as the main allergic comorbidities. Regarding laboratory data, most protein fractions had values ≤ 10 kU/L in both groups. It was found that maternal age ($p = 0.006$) and age of introduction of formula ($p = 0.020$) were statistically significant in the group of patients tolerant to processed foods. **Conclusions:** It was observed that maternal age ($p = 0.006$) and age of introduction of formula ($p = 0.020$) were statistically significant in the group of patients tolerant to processed foods. Laboratory data were proportionally distributed across the two groups, with a higher frequency of values lower than or equal to 10 kU/L for all CMP fractions, with no statistical significance between the groups. Similar population studies in IgE-mediated CMPA populations are important to better characterize this phenotype and optimize diagnostic tools and treatment protocols. The role of baked therapy is also noteworthy, as it helps patients to develop tolerance to different presentations of CMP more quickly, improving their quality of life.

Keywords: Hypersensitivity, Milk hypersensitivity, Child.

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INTRODUCTION

The prevalence and incidence of food allergy has increased in recent years. Among food allergies, cow's milk protein allergy (CMPA) is the most frequent in the pediatric population, affecting 2 to 5% of children under two years of age[1–3]. The epidemiology of CMPA is influenced by characteristics of the population such as genetic, environmental, nutritional and social factors[4,5]. Therefore, there are different prevalence rates: 2-3% for infants up to one year of age and 1% for children up to six years of age, according to ESPGHAN; and 1-17.5% for preschool children, according to the DRACMA Guideline[4,5].

This condition has several clinical manifestations, and can lead to severe conditions, such as anaphylaxis[1,6]. Most patients develop tolerance to food allergens in childhood, with only 10% remaining intolerant until adulthood[6]. The natural course of CMPA has been changing, with reports of longer periods for the development of tolerance and lower resolution rates. About 50% of children with CMPA will develop tolerance before 5 years of age, and 75% will be tolerant in adolescence[7].

Cow's milk is composed of several classes of polypeptide chains, such as casein, which represents 75 - 85% of milk proteins, and whey soluble proteins, with beta-lactoglobulin and alpha-lactalbumin as the main groups, representing about 15-22% of total milk proteins, all of which are potential allergens[8,9]. After exposure to cow's milk, genetically predisposed children develop specific Immunoglobulin E (IgE) antibodies against its components, becoming sensitized. In a second encounter with these proteins, these antibodies bind to epitopes on the proteins and trigger allergic reactions[6,10].

Epitopes can be linear or conformational. The ability to develop tolerance is related to the reduction in the amount of IgE and the binding affinity of IgE to specific epitopes. The casein group has a linear conformation and tends to be associated with the persistence of allergy over time. The group of whey proteins has conformational epitopes, allowing the individual to tolerate the consumption of small amounts of milk with altered tertiary structure (cooked or partially hydrolyzed)[8,9].

The proteins that make up cow's milk can have their properties altered by food processing techniques[8,11]. Linear epitopes are thermostable and resistant to temperature changes, which gives them a higher allergenic potential. The loss of the three-dimensional structure of protein when denatured by heat destroys conformational epitopes, limiting the binding of specific IgE. Therefore, thermal processing is a way to reduce the allergenic potential of some foods[4,8,11]. In addition, the allergenicity of milk proteins can also be reduced by the interaction with other food matrices, such as wheat in a cake[2].

Literature reports show that children with transient IgE-mediated CMPA have a higher amount of IgE antibodies for conformational epitopes like alpha-lactalbumin, beta-lactoglobulin and lactoferrin, while children with persistent IgE-mediated CMPA have a higher proportion of IgE antibodies for linear epitopes without defined cut-offs values, such as casein and albumin[6,11].

The oral food challenge (OFC) is considered the gold standard to diagnose food allergy and to assess the development of food tolerance[9]. The test can help restoring the quality of life of patients on restrictive diets, who have unpleasant experiences with the adverse reactions of CMPA[13,14]. During the natural course of CMPA, patients can develop tolerance to processed milk, which can become an important source of cow's milk protein (CMP) for these children after a favorable OFC[6,11].

Tolerance to the OFC with raw and processed milk seems to reveal two types of phenotypes of patients with CMPA: those who tolerate processed foods and those who do not[1,12,15]. Furthermore, children with CMPA who tolerate processed dairy products seem to overcome their milk allergy more quickly than those who do not[13]. In addition, *baked therapy* stimulates the inclusion of baked-milk products even after a negative OFC for processed CMP, as it can accelerate the development of tolerance[16–18].

To date, there are no defined cut-off values or clinical data to differentiate the profile of IgE-mediated CMPA patients who are tolerant to processed or raw foods[1,13,14,19]. The objective of this study is to describe the population of children with IgE-mediated CMPA tolerant to processed or raw CMP in

the OFC, comparing their clinical, epidemiological and laboratory characteristics and evaluating possible predictors of outcomes associated with these different presentations of CMP.

METHODS

This is a cross-sectional study conducted at the allergy clinic of the Albert Sabin Children's Hospital (HIAS) in the city of Fortaleza-Ceará. Data was collected from October 2018 to September 2019.

The project was approved by the Albert Sabin Children's Hospital (HIAS) ethics committee under the approval number: 2,717,112. Those responsible for the children were interviewed before the OFC, when the scope of the study was explained, and the parents or guardians signed the informed consent document (ICD) for children from 0 to 9 years old or the consent document (CD) for children from 10 to 18 years old.

The questionnaire was filled with epidemiological, clinical and laboratory data found in each patient's medical records. The inclusion criteria were: children diagnosed with IgE-mediated CMPA, up to 18 years of age, with no accidental exposure or no reactions to accidental exposures in the last 6 months. Participants were oriented to follow a CM-free diet and informed that they would undergo an OFC. Exclusion criteria were breastfed infants, children without a definitive clinical and laboratory diagnosis of CMPA, and patients who did not do the OFC (missing patient, recent use of antihistamines or current infection) or did not complete it (refusal to consume the food, subjective symptoms).

Specific IgEs measurement

The specific IgEs for cow's milk alpha-lactoalbumin, beta-lactoglobulin and casein (ImmunoCAP, Phadia, MA, USA) collected by the HIAS support laboratory in a standardized way were analyzed. For the statistical analysis, a cut-off value greater than or equal to 10 and lower than 10 was adopted, based on the frequencies observed in the HIAS service. Exams performed up to three months before data collection were considered.

Oral Food Chalenge (OFC)

The tolerance of children diagnosed with IgE-mediated CMPA was evaluated through the OFC, using different presentations of CMP according to previous clinical history of tolerance in domestic exposure or a favorable evolution of laboratory tests (specific IgEs for cow's milk, casein, alpha-lactalbumin and beta-lactoglobulin lower than values found in previous tests). The tests were performed in a hospital environment, following the HIAS protocol adapted to the guidelines of the American Academy of Allergy, Asthma and Immunology (AAAI) and the European Academy of Allergy and Clinical Immunology (EAACI).[20,21]. Parents were previously informed about the steps of the test and signed an informed consent form. CMP was administered in raw or processed form (baked, in the form of a cookie or cake, in the minimum amounts established by the Brazilian Consensus on Food Allergy[3,22]) and in increasing amounts, according to the patient's acceptance. After food intake, patients were observed for up to two hours in a hospital environment, and oriented to return in case of late reactions. If the patient presented any symptoms of allergic reaction, the test was considered positive and interrupted to support the patient. The OFC was not interrupted in case of subjective symptoms (abdominal pain, food refusal, occasional sneezing, isolated perioral contact dermatitis, among others).

STATISTICAL ANALYSIS

The data obtained were analyzed according to the absolute (n) and relative (%) frequencies of qualitative variables. The chi-square (x2) test or Fisher's exact test were used to analyze the differences between categorical variables. Multinomial logistic regression analysis was conducted to obtain the odds ratio (OR) and 95% confidence interval (CI) for the variables with statistically significant results in the chi-square test (x2) or p-value<0.05 in the Fischer's exact test. The results were presented in descriptive and association tables.

The Shapiro-Wilk test was used to analyze the normality of data distribution for quantitative variables. Student's t test was used for variables with parametric distribution. The Mann-Whitney test was used for non-parametric variables. A probability level of $p<0.05$ was adopted for all inferential procedures. All statistical analyzes were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

During the research period, 82 children who underwent the OFC to assess tolerance to CMP were evaluated by a questionnaire (QE1). Of these, 21 patients were excluded for having a final diagnosis of non-IgE-mediated or mixed CMPA.

In a second moment, after reviewing the data (questionnaire 2 - QE2), 2 patients were excluded for inconclusive and/or absent OFC results, leaving a sample of 59 children. Finally, 10 children were classified as non-tolerant in the OFC and were excluded from the study, resulting in a final sample of 49 children with IgE-mediated CMPA tolerant to the OFC with processed or raw foods, as shown in Figure 1.

IgE-mediated children tolerant to raw CMP

Tables 1, 2 and 3 summarize clinical and laboratory data for this group, composed of 30 children with a mean age of 33 months (min.:19-max.:84), of which 18 (60%) were male and 22 (73.3%) were of mixed ethnicity. As for the quantitative data, the mean weight at birth was 3.5 kg (min.:2.19-max.:5.25) and the mean height at birth was 50 cm (min.:39-max.:57).

Most children were born at term (80%) and without complications during pregnancy (58.3%) or delivery (70%). The mean maternal age was 32 years (min.:18 and max.:43) and most mothers had completed high school (43.3%). The main age of onset of CMPA symptoms was 1 to 6 months (76.7%). Antibiotic use had two frequency peaks, with 30% of children on antibiotic therapy between 1 month and 6 months of age and 30% between 12 and 18 months of age.

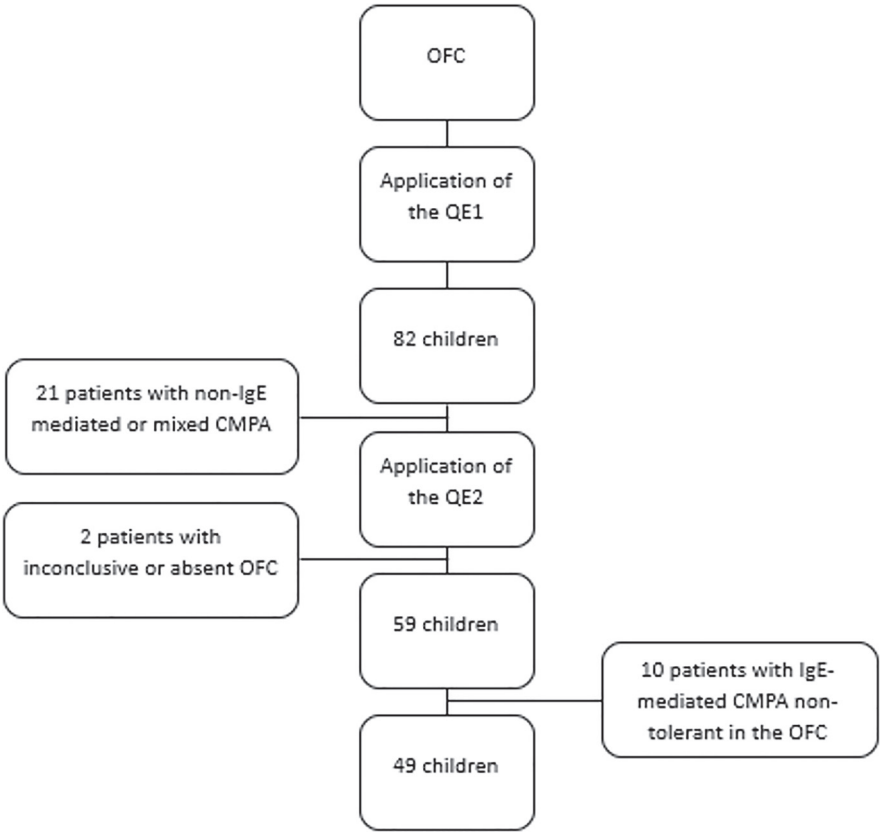

Figure 1. Sample collection flowchart.

Table 1. Stratification of clinical variables by IgE-mediated patient's tolerance to processed or raw foods.

Variables	IgE-mediated children tolerant to raw CMP (n=30)		IgE-mediated children tolerant to processed CMP (n=19)		*p*
	N	%	N	%	
Gender					
Male	18	60,0	11	57,9	1.000
Female	12	40,0	8	42,1	
Ethnicity					
White	8	26,7	6	31,6	
Mixed ethnicity	22	73,3	13	68,4	0.754
Black	0	0,0	0	0,0	
Mother's level of education					
Incomplete Elementary Education	1	3,3	3	10,5	
Incomplete Secondary Education	3	10,0	1	5,3	
Complete Secondary Education	13	43,3	9	47,4	0.841
Incomplete Higher Education	5	16,7	3	15,8	
Complete Higher Education	8	26,7	4	21,1	
Type of Delivery					
Normal	5	16,7	3	15,8	1.000
C-section	25	83,3	16	84,2	
Childbirth Complications					
Yes	9	30,0	4	21,1	0.530
No	21	70,0	15	78,9	
Gestational Age at Delivery					
Less than 37 weeks	3	10,0	1	5,6	
37 to 41 weeks	24	80,0	14	77,8	0.754
More than 41 weeks	3	10,0	3	16,7	
Pregnancy Complications					
Yes	10	41,7	3	20,0	0.295
No	14	58,3	12	80,0	
Types of Pregnancy Complications					
Fever without focus	1	10,0	0	0,0	
Urinary tract infection	7	70,0	0	0,0	
Respiratory tract infection	1	10,0	1	50,0	0.152
Anogenital infection	1	10,0	0	0,0	
Skin infection	0	0,0	1	50,0	
Time of Exclusive Breastfeeding					
< 1 Month	2	6,7	0	0,0	0.180
Between 1 and 4 months	8	26,7	4	21,1	
Between 4 to 6 months	18	60,0	13	68,4	
Over 6 months	0	0,0	2	10,5	
Never breastfed	2	6,7	0	0,0	
Age of Introduction of Formula					
< 1 Month	9	30,0	2	10,5	**0.020**
Between 1 and 4 months	9	30,0	4	21,1	
Between 4 to 6 months	10	33,3	5	26,3	
Over 6 months	2	6,7	8	42,1	
Type of Formula used					
Whole cow's milk	3	10,0	1	5,3	
Infant formula	16	53,3	7	36,8	
Soy infant formula	1	3,3	4	21,1	0.269
Partially hydrolyzed formula	5	16,7	2	10,5	
Extensively hydrolyzed formula with lactose	5	16,7	5	26,3	
Other formulas	0	0,0	0	0,0	

continue...

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Variables	IgE-mediated children tolerant to raw CMP (n=30)		IgE-mediated children tolerant to processed CMP (n=19)		*p*
	N	%	N	%	
Age of Food Introduction					
>6 months	6	20,0	5	26,3	0.729
Between 4 and 6 months	24	80,0	14	73,7	
Age of Antibiotic Use					
Never used antibiotics	2	6,7	4	21,1	**0.011**
< 1 Month	3	10,0	1	5,3	
Between 1 and 6 months	9	30,0	0	0,0	
Between 6 and 12 months	4	13,3	8	42,1	
Between 12 and 18 months	9	30,0	6	31,6	
Between 18 and 24 months	3	10,0	0	0,0	
Family History of Food Allergy					
Yes	22	73,3	13	68,4	0.754
No	8	26,7	6	31,6	
Relatives with food allergy					
Father	13	59,1	5	38,5	
Mother	6	27,3	5	38,5	0.579
Siblings	3	13,6	3	23,1	
Family history of other allergies					
Medication allergy	0	0,0	1	6,7	
Skin allergy	20	83,3	12	80,0	0.613
Respiratory allergy	4	16,7	2	13,3	
Food allergy	0	0,0	0	0,0	
Other allergies of the children					
Medication allergy	1	5,6	2	14,3	
Skin allergy	3	16,7	2	14,3	0.907
Respiratory allergy	7	38,9	5	35,7	
Food allergy	7	38,9	5	35,7	
Age of onset of CMPA Symptoms					
< 1 month	3	10,0	1	5,3	
Between 1 and 6 months	23	76,7	13	68,4	0.450
> 6 months to 1 year	3	10,0	5	26,3	
Over 1 year	1	3,3	0	0,0	

Abbreviations: N = number of patients in the sample; p = p value

Table 2. Quantitative variables according to IgE-mediated patient's tolerance to processed or raw foods.

Variables	IgE Mediated – OFC Tolerance		*p*
	Raw Food	Processed Food	
	Mn±SD (Min-Max)	Mn±SD (Min-Max)	
Variables	33±17 (19-84)	27±37 (2-143)	0.340
Variables	32±6 (18-43)	35±4 (26-42)	**0.006**
Variables	3,5±0,72 (2,19-5,25)	3,25±0,47 (2,50-4,08)	0.206
Variables	50±4 (39-57)	50±2 (45-56)	0.836
Variables	13,4±5,9 (8,7-39,8)	15,6±9,5 (10,2-52,0)	0.101
Variables	90±15,6 (74-143)	99±18,5 (81-153)	0.188
Variables	16±2 (13-19)	16±2 (13-22)	0.397

Abbreviations: Mn = mean; SD = standard deviation; Min = minimum; Max = maximum; p = *p-value*

Table 3. Stratification of laboratory variables by IgE-mediated patient's tolerance to processed or raw food.

Variables	IgE-mediated children tolerant to raw CMP (n=30)		IgE-mediated children tolerant to processed CMP (n=19)		*p*
	N	%	N	%	
Total IgE for Cow's Milk					
≤10	24	85,7	10	58,8	0.072
>10	4	14,3	7	41,2	
IgE for Alpha-Lactalbumin					
≤10	27	93,1	14	87,5	0.608
>10	2	6,9	2	12,5	
IgE for beta-lactoglobulin					
≤10	27	96,4	14	82,4	0.281
>10	1	3,6	3	17,6	
IgE for Casein					
≤10	23	93,1	14	82,4	0.343
>10	2	6,9	3	17,6	

Abbreviations: N = number of patients in the sample; p = p-value

Regarding food, most children were exclusively breastfed for 4 to 6 months (60%) and started complementary feeding between 4 and 6 months (33.3%), with the main type being infant formula (53.3%). The age of food introduction was between 4 and 6 months (80%).

Most children had a family history of allergy (73%), mainly among fathers (59.1%), followed by mothers (27.3%) and siblings (13.6%). The family members' allergies described were mainly of medication (83.3%), followed by respiratory allergies (16.7%). The other allergies of the patients include respiratory (38.9%), food (38.9%), skin (16.7%), and medication allergy (5.6%). Clinical and quantitative data did not show statistical significance.

The laboratory data in Table 3 show a higher frequency of values lower than or equal to 10 kU/L for all cow's milk protein fractions in this group, with total IgE for cow's milk 85.7%, alpha-lactalbumin 85.7%, beta-lactoglobulin 96.4% and casein 93.1%.

The p-value was not significant for the relationship between these values and the type of food with a favorable outcome in the OFC (respectively, 0.072, 0.608, 0.281, 0.343)

IgE-mediated children tolerant to processed CMP

Tables 1, 2 and 3 summarize clinical and laboratory data for this group, composed of 19 children with a mean age of 27 months (min.:2 max.:143), of which 11 (57.9%) were male and 13 (68.4%) were of mixed ethnicity. The mean weight at birth was 3.25 kg (min.:2.50-max.:4.08) and the mean height at birth was 50 cm (min.:45-max.:56), as shown in table 2.

Most children of the group were born at term (77.8%) by c-section (84.2%), without complications during pregnancy (80%) or delivery (78.9%). The most frequent pregnancy complications were respiratory tract infection (50%) and skin infection (50%). The mean maternal age was 35 years (min.:26 max.:42), with a statistically significant association between advanced maternal age and tolerance to processed foods. (p = 0.06), as seen in table 3. Most mothers had completed high school (47.4%). For most patients in this group, the age of onset of CMPA symptoms was 1 to 6 months (68.4%).

The data on feeding of this group were similar to the data of patients tolerant to raw foods: most children were exclusively breastfed for 4 to 6 months (68.4%), the most used complementary feeding method was infant formula (36.8%), and the age of food introduction was between 4 and 6 months (73.7%). Data on the age of introduction of formula were significant (p = 0.020), showing a correlation between the introduction of formula after 6 months of age and a favorable outcome with processed foods.

Most family members of this group had a history of allergy (68.4%), with father (38.5%) and mother (38.5%) being the most cited, followed by siblings (23.1%). The most frequent allergies were skin (80%), respiratory (13.3%) and medication allergy (6.7%). The other allergies mentioned in this group were respiratory (35.7%), food (35.7%), medication (14.3%) and skin allergy (14.3%).

The laboratory data presented on table 3 indicate a higher frequency of values lower than or equal to 10 kU/L for all cow's milk protein fractions in this group, with total IgE for cow's milk 58.8%, alpha-lactalbumin 87.5%, beta-lactoglobulin 82.4% and casein 82.4%. The p-value was not significant for the relationship between these values and tolerance to processed food (0.072, 0.608, 0.281, 0.343, respectively).

DISCUSSION

CMPA is a temporary condition for most patients, lasting up to the third year of age. However, 25% of patients develop tolerance before 12 months of age, 50% before 2 years of age and 85% are tolerant before 3 years of age[2,4,14,23]. The proteins that make up cow's milk may be altered by food processing techniques, which make some types of processed foods tolerable for children with CMPA[4,8,11]. Patients have a tolerance of 65 to 83% to processed milk, indicating an earlier acceptance of this CMP, which allows a variety of foods to be used, improving the quality of life of these patients[12,15,24].

IgE-mediated CMPA patients can have mild or more severe clinical manifestations (urticaria, asthma, diarrhea, intestinal bleeding, anaphylaxis), even in diets with only traces of CMP, which makes parents and patients constantly fearful of food consumption. Therefore, new sources of milk and calcium for these children can make CMPA more tolerable, reduce the risk of nutritional impairment and make the diet less onerous for parents[14,25].

In this study, we sought to describe two populations of patients with IgE-mediated CMPA tolerant to different types of CMP processing, aiming to find clinical and laboratory data that characterize these phenotypes.

The results showed a higher percentage of children with tolerance to raw milk (75%), contrary to data from other studies, which report a higher rate of tolerance to processed foods, between 63 and 85%[1]. This may be due to the small sample or the sample selection method, which may have limited patient variability.

The two groups analyzed had similar clinical data, including mean age, gender, ethnicity, pregnancy and childbirth data, age of onset of CMPA symptoms, duration of breastfeeding, use of complementary feeding and some family history data, but no statistical relevance[26–30].

Some results are in accordance with data described in the literature, such as the association between tolerance to processed foods and risk factors such as cesarean delivery (84.2%), time of exclusive breastfeeding between 4 and 6 months (68.4%), early introduction of food (73.7%), family history of food allergy (68.4%) and onset of CMPA symptoms between 1 and 6 months (68.4%) and the high frequency of protective factors among patients tolerant to raw foods, such as male children (60%) and lower rates of complications during pregnancy (58.3%) and childbirth (70%)[1,3,29,30].

Some data, such as the high rate of cesarean deliveries among children tolerant to raw milk and low levels of IgE in children tolerant to processed foods, however, diverge from other studies. This is probably associated with variations typical of the study population and the high prevalence of cesarean deliveries in the Brazilian population. This contributes to the description of specific characteristic of each population. Therefore, further studies should be conducted to establish the clinical correlations and the OFC outcome for this specific population.

In the group of patients tolerant to processed milk, advanced maternal age was statistically associated with tolerance to processed foods ($p = 0.006$), as seen in table 3. Advanced maternal age was discussed in other population studies, which suggested hormonal factors and higher genetic susceptibility to developing allergies[29,31].

The data showed ($p = 0.020$) a correlation between the introduction of formula after 6 months of age and a favorable outcome with processed milk. The use of infant formula or even other dairy products is associated with the development of atopy, especially when done early (before 6 months of age). Exclusive breastfeeding up to that age is the main protective factor, as shown by the main studies on CMPA[4,6].

In our study, the introduction of formula after the age of 6 months was associated with tolerance to processed milk. It is possible to suggest that a later introduction of formula can also be associated with a longer time for the development of tolerance to raw milk; however, it is important to establish new age groups to correlate with this phenotype.

Laboratory data were proportionally distributed across the two groups, with a higher frequency of values lower than or equal to 10 kU/L for all cow's milk protein fractions, with no statistical significance between the groups. Other studies have suggested several different cut-off values for IgE and for the skin prick test.

Kawahara et al, 2019 suggested cut-off values of 28.3 versus 7.7 AU/mL ($p < 0.0001$) for severe and non-severe reaction CMPA patients, respectively[30]. On the other hand, a Brazilian study carried out at the Federal University of Sergipe, compared a group of children with CMPA to children without allergy and found values capable of predicting clinical reactivity to CM at 5.17kUA/L for specific serum IgE and 3.5 mm for mean papule diameter[33]. Most of these studies show different values and cut-off points, probably influenced by factors of the sample itself (environment, genetics, type of exams, study design, among others)[27,30,33].

Factors such as family history of atopy and more severe allergic manifestations, higher prick-test diameters, higher specific IgE values, especially casein IgE and cow's milk IgE, and the presence of other allergies are associated with the persistence of CMPA beyond 60 months of age[27,34,35]. It is also suggested that high levels of IgE are associated with a low response to immunotherapy in the treatment of food allergy in patients with persistent CMPA[36-38].

This study is important for being the first, to our knowledge, to describe a population of IgE-mediated CMPA patients treated in the state of Ceará, differentiating two profiles of tolerance to CMP based on clinical and laboratory parameters.

Similar population-based studies have been carried out with different populations with IgE-mediated CMPA to better characterize this phenotype and assist in the discovery of new diagnostic tools and treatment protocols[39-41]. The description of these two profiles of IgE-mediated CMPA patients is also important to call attention to the role of *baked therapy*, which helps patients to develop tolerance to different presentations of CMP in a faster way, improving their quality of life.

CONCLUSION

In our study, maternal age ($p = 0.06$) and the age of introduction of formula ($p = 0.020$) were statistically significant in the group of patients tolerant to processed milk.

Laboratory data were proportionally distributed across the two groups, with a higher frequency of values lower than or equal to 10 kU/L for all CMP fractions, with no statistical significance between the groups.

Baked therapy seems to help IgE-mediated CMPA patients to develop tolerance to different presentations of CMP in a faster way, improving the quality of life of these patients.

This is the first study to date to describe a pediatric population with CMPA from Ceará according to their tolerance to raw and processed CMP. Our results suggest new threshold values for laboratory tests, which should preferably be compared in a case-control study, to define cut-off values according to sensitivity and specificity data.

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